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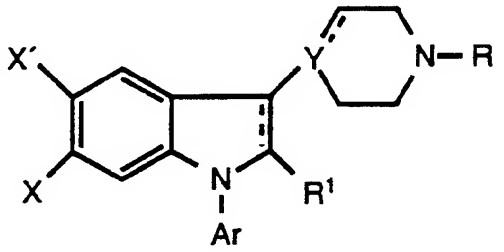

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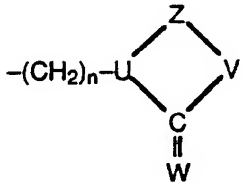

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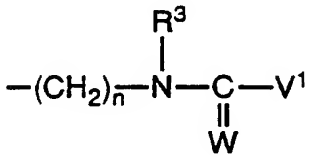

(Ib)

(57) Abstract

6-and/or 2-substituted 1-arylindole derivative of general formula (I), where Ar is optionally substituted phenyl or a hetero aromatic group; X and X' are hydrogen, halogen, alkyl, alkoxy, hydroxy, alkylthio, alkylsulfonyl, alkyl- or dialkylamino, cyano, trifluoromethyl, or trifluoromethylthio; or X and X' are linked to constitute a 5-7 membered carbocyclic ring; R^1 is hydrogen, or lower alkyl, provided that when X is hydrogen or fluoro, then R^1 is not hydrogen; Y is nitrogen or carbon; R is hydrogen, alkyl, alkenyl, cycloalkyl, or cycloalkylmethyl, or R is a substituent of formula (1a) or (1b), wherein n is 2-6; W is oxygen or sulfur; U is nitrogen or carbon; Z is $-(CH_2)_m-$, -CH=CH-, $-COCH_2-$, $-CSCH_2-$ or 1,2-phenylene; V is oxygen, sulfur, CH_2 or NR^2; V^1 is $-O-R^4$, $-S-R^4$, $-CHR^4R^5$ or $-NR^4R^5$; and R^3, R^4 and R^5 are hydrogen, alkyl, alkenyl, cycloalkyl, or cycloalkylmethyl; inhibit the firing of spontaneously active dopamine neurones in the ventral tegmental area of the brain and are thus useful for the treatment of psychoses in humans.

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TREATMENT OF PSYCHOSES

Use of arylindole derivatives for the treatment of psychoses

The present invention relates to the use of certain 6- and/or 2-substituted 1-arylindole derivatives or salts or prodrugs thereof for the manufacture of a pharmaceutical preparation for the treatment of psychoses.

BACKGROUND OF THE INVENTION

Damping of dopamine (DA) overactivity by the use of DA receptor blocking drugs is today the most important principle in the treatment of schizophrenia, more particularly the positive symptoms thereof. "Classical neuroleptics" such as haloperidol, cis(Z)-flupentixol and chlorpromazine are believed to induce antipsychotic effect via DA receptor blockade. Pharmacologically, such compounds antagonize stereotypies induced by dopaminergic compounds (i.e. methylphenidate, apomorphine, amphetamine) in mice or rats and they inhibit pergolide-induced circling behavior in rats with unilateral 6-OHDA lesions. Unfortunately, the incidence of severe extrapyramidal side effects (EPS) (dystonia, akathisia and parkinsonism) is very frequent in long term treatment with these neuroleptics and causes great concern among clinicians. The EPS are difficult to treat, and unsuccessful treatment often leads to poor medication compliance. Some of these neurological side effects, which generally involve involuntary movement disorders, have been correlated to the propensity of the drugs to induce catalepsy in rats (Arnt. et al., Neuropharmacology, **1981**, *20*, 1331-1334).

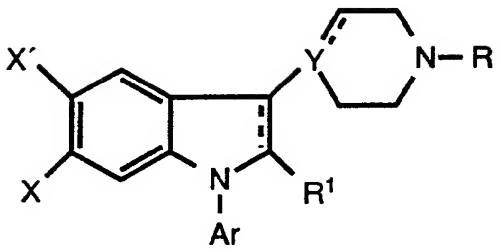
A few compounds, which do not produce EPS and which are effective in the treatment of schizophrenic disorders, are termed "atypical neuroleptics". Clozapine is such a drug. Clozapine is an effective antipsychotic in man but, due to the risk of drug induced agranulocytosis, regular monitoring of blood parameters is required, and its use is therefore costly and restricted. Pharmacologically clozapine induces no catalepsy in rats, neither does it inhibit stereotypies induced by dopaminergic compounds in rodents. Clozapine blocks central cholinergic, serotonergic and

noradrenergic receptors in animal studies.

In recent years several reports have suggested that inhibition of the spontaneous activity of DA neurones in the *ventral tegmental area* (VTA) in the rat brain upon repeated treatment with a drug is indicative of the antipsychotic potential of the drug, whereas inhibition of the activity in *substantia nigra pars compacta* (SNC) should account for the development of EPS. "Classical neuroleptics" are active in both areas in the same dose range while "atypical neuroleptics" mainly inactive DA neurones in the VTA. Clozapine has been shown to be active only in the VTA (Bunney and Grace, *Life Science*, **1978**, *25*, 1715-1725, White and Wang, *Science*, **1983**, *221*, 1054-1057, Chiodo and Bunney, *J.Neuroscience*, **1985**, *5*, 2539-2544, Skarsfeldt, *Life Science*, **1988**, *42*, 1037-1044).

U.S.Patent No. 4,710,500, corresponding to European Patent No. 0200322, discloses a class of optionally 5-substituted 1-aryl-3-piperidinyl, 1-aryl-3-(1,2,3,6-tetrahydropyridinyl)- or 1-aryl-3-piperazinylindole derivatives having potent 5-HT2 antagonistic activity, and many of them additionally having potent DA D_2-antagonistic activity *in vivo* . Previously, one of the compounds known from said patent, i.e. sertindole, 5-chloro-1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)-ethyl]-4-piperidyl]-1H-indole, which is a 5-HT_2 antagonist substantially without DA D_2-antagonistic activity *in vivo*, was surprisingly found to inhibit the firing of DA neurones in the VTA og the brain (cf. our own EP-A1-0392959). However, said patent publication also shows that other very closely related 5-HT_2 antagonists known from U.S.Patent No. 4,710,500 do not inhibit the firing of DA neurones.

Our own copending European Patent Application No. 916010055.5 published as EP-A2-0465398 discloses a class of 6-substituted and/or 2-alkyl substituted indole and 2,3-dihydroindole derivatives having the general Formula I



I.

where Ar is phenyl, phenyl substituted with one or more substituents selected from halogen, lower alkyl, lower alkoxy, hydroxy, trifluoromethyl, and cyano, or a hetero aromatic group selected from 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-oxazolyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl;

the dotted lines indicate optional bonds;

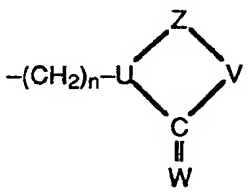
X is hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy, lower alkylthio, lower alkylsulfonyl, lower alkyl- or dialkylamino, cyano, trifluoromethyl, or trifluoromethylthio;

X´ is a substituent taken from the X-substituents above; or
X and X´ are linked to constitute a 5-7 membered carbocyclic ring;

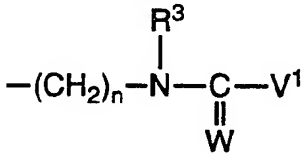
R^1 is hydrogen, lower alkyl or lower alkyl substituted with one or two hydroxy groups, provided that when X is hydrogen or fluoro, then R^1 is not hydrogen;

Y is nitrogen or carbon, provided that when the dotted line emanating from Y indicates a bond, then Y is carbon;

R is hydrogen, or lower alkyl, lower alkenyl, cycloalkyl, or cycloalkylmethyl, each optionally substituted with one or two hydroxy groups, any hydroxy group present being optionally esterified with an aliphatic carboxylic acid having from two to twentyfour carbon atoms inclusive, or R is a substituent of the formula 1a or **1b** :



1a.



1b.

wherein n is an integer from 2 - 6, inclusive;
W is oxygen or sulfur;
U is nitrogen or carbon;
Z is selected from $-(CH_2)_m-$, m being 2 or 3, -CH=CH- , $-COCH_2-$, $-CSCH_2-$, 1,2-phenylene and 1,2-phenylene substituted with halogen or trifluoromethyl;

V is selected from oxygen, sulfur, CH_2, and NR^2 , wherein R^2 is hydrogen, lower alkyl, lower alkenyl, a cycloalkyl group, a cycloalkylmethyl group, lower alkyl substituted with one or two hydroxy groups, and lower alkenyl substituted with one or two hydroxy groups;
V^1 is $-O-R^4$, $-S-R^4$, $-CHR^4R^5$ or $-NR^4R^5$;
R^3 is hydrogen, lower alkyl, lower alkenyl, a cycloalkyl group, a cycloalkylmethyl group, lower alkyl substituted with one or two hydroxy groups, and lower alkenyl substituted with one or two hydroxy groups; and
R^4 and R^5 are independently selected from the R^3-substituents.

In pharmacological tests said compounds were found to be highly potent 5-HT_2 antagonists having long duration of action and, accordingly, they were claimed to be useful in the treatment of anxiety, depression, sleep disturbances, migraine, negative symptoms of schizophrenia, and Parkinson´s disease. Furthermore, they were found to lack dopamine receptor affinity and to be substantially inactive with respect to acute DA antagonistic activity *in vivo*. The tests used were:
a) Inhibition of ^{3}H-ketanserin binding to 5-HT_2 receptors in rat cortex *in vitro,* which is a test for affinity of drugs for 5-HT_2 receptors *in vitro.*
b) Quipazine antagonism which is a test for 5-HT_2 antagonistic effect *in vivo* based on the testing of the ability of drugs to inhibit quipazine-induced head twitches in rats.
c) Inhibition of ^{3}H-spiperone binding to DA D_2 receptors in rat corpus striatum *in vitro* which is a test for affinity of drugs for DA D_2 receptors *in vitro.*
d) Antagonism of pergolide-induced circling behavior in rats with unilateral 6-OHDA lesions, which is an extremely sensitive test for acute central DA antagonistic effect *in vivo.*

So, in view of the fact that it is known that affinities of antipsychotic drugs for 5-HT_2 receptors do not correlate to effects on positive symptoms of schizophrenia (Peroutka, S.J. and Snyder,S.H.: Relationship of neuroleptic drug effects at brain dopamine, serotonin, alpha-adrenergic, and histamine receptors to clinical potency, *Am. J. Psychiatry*, **1980,** *137*, 1518-1522), they were believed to be without antipsychotic effects.

SUMMARY OF THE INVENTION

Surprisingly, it has now been found that the 6-substituted and/or 2-alkyl substituted indole and 2,3-dihydroindole derivatives having the above general Formula **I** inhibits the firing of DA neurones in VTA in rats.

Accordingly, the present invention provides the use of a compound having the above defined general Formula **I** or a pharmaceutically acceptable acid addition salt thereof, for the manufacture of a pharmaceutical composition for the treatment of psychosis in humans.

The use of stereoisomers and prodrugs of the 6-substituted or 2-alkyl substituted 2,3-dihydroindole derivatives of Formula **I** is also embraced by this invention.

In the context of the present invention and the definition of Formula **I** the terms lower alkyl, lower alkoxy, lower alkylthio and lower alkylsulfonyl designate such straight chained or branched groups having from one to four carbon atoms inclusive. Exemplary of such groups are methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2-methyl-1-propyl, methoxy, ethoxy,1-propoxy, 2-propoxy, methylthio, ethylthio, 1-propylthio, 2-propylthio, methylsulfonyl, ethylsulphonyl, or the like. The term lower alkeny refers to such groups having from two to four carbon atoms inclusive.

Cycloalkyl is such a group comprising 3–8 carbonatoms, and halogen means fluoro, chloro, bromo or iodo.

The psychoses to be treated are psychosis in connection with schizophrenia (positive symptoms of schizophrenia) and other psychoses and related deseases such as mania etc.

An effective daily dose of the compound of the invention, or a pharmaceutically acceptable salt thereof, is from 0.01 to 10.0 mg/kg. The daily dose is administered in one or more subdoses and, accordingly, a unit dose of the compound or of the salt thereof is from 0.10 to 200 mg.

The compositions of the invention may exist in forms to be administered both orally or parenterally, for example in the form of tablets, capsules, powders, syrups or solutions for injection.

Preferred compounds used according to the invention are:
6-chloro-1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole, Comp. **1**, and
6-chloro-1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, Comp. **2**,
5-chloro-1-(4-fluorophenyl)-2-methyl-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole, Comp. **3**.

As shown by the test for inhibition of pergolide induced rotations in rats with unilateral 6-OHDA lesions in our prior EP-A2-0465398, the compounds used in the present invention do not show acute antidopaminergic activity *in vivo* and as shown in the ^{3}H-spiperone binding test they have substantially no affinity for dopamine receptors *in vitro*. Accordingly, they were believed to be without antipsychotic effecs.

However, they have now unexpectedly been found to inhibit the firing of spontaneously active DA neurones in the VTA of the brain upon repeated treatment as measured electrophysiologically, and thus to have antipsychotic potential.

The compounds have been found selectively and partially to inhibit the firing of the DA neurones in the VTA substantially without inhibiting the firing of the DA neurones in the SNC area. Since inhibiting effect in the SNC area is indicative of neuro-

logical side effects these compounds are believed to be substantially without such side effects. So, they have been demonstrated to be very promising drugs for the treatment of psychoses (i.e. positive symptoms of schizophrenia and psychosis of other genesis).

As mentioned above and already shown in our prior EP-A2-0465398 the compounds used in the present invention have potent central 5-HT_2 antagonistic activity. Since such activity is indicative of i.a. effect on negative symptoms of schizophrenia and on quality of sleep, the compositions of the invention have the further advantage of alleviating or relieving the negative symptoms of schizophrenia and/or improving the quality of sleep in a schizophrenic patient. Such effects are highly desired in connection with antipsychotic treatment.

The compounds of the general Formula I may be synthesized by methods according to our prior EP-A2-0465398, and specific compounds of Formula I are disclosed therein.

The pharmaceutically acceptable acid addition salts of the compounds may be formed by reaction with non-toxic organic or inorganic acids in an aqueous miscible solvent, such as acetone or ethanol, and subsequent isolation of the salt by concentration and cooling or by reaction with an excess of the acid in aqueous immiscible solvent, such as ethyl ether or chloroform, with the desired salt separating directly.

Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, embonic, succinic, oxalic, bis methylene-salicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids as well as the 8-halotheophyllines, for example 8-bromo-theophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. Of course, these salts may also be prepared by the classical method of double decomposition of appropriate salts, which is well known to the art.

In the following the invention is further illustrated by way of examples with references to the drawings in which:

Fig. **1** : Shows the inhibiting effect of Compound No **1** of the invention on the firing of neurones in the VTA and the SNC areas of the brain, respectively.

Fig. **2** : Shows the inhibiting effect of Compound No **2** of the invention on the firing of neurones in the VTA and the SNC areas of the brain, respectively.

Fig. **3** : Shows the inhibiting effect of the reference compound haloperidol on the firing of neurones in the VTA and the SNC areas of the brain, respectively.

Fig. **4** : Shows the inhibiting effect of the reference compound clozapine on the firing of neurones in the VTA and the SNC areas of the brain, respectively.

PHARMACOLOGY

Compounds used in the invention were tested according to a reliable and well known pharmacological method as follows:

Inhibition of DA cell firing in VTA and SNC areas

This test model is used to examine the effects on spontaneously active DA neurones in VTA and SNC upon repeated oral treatment. Inhibition of the number of active DA neurones in VTA indicates an antipsychotic effect of a compound, while inhibition of the number of active DA neurones in SNC accounts for the development of neurological side effects.

For further information see Skarsfeldt, T.: Eur. J. Pharmacol. 145, 239-243 (1988) which information is incorporated herein by reference.

Rats weighing 250 g at the start of the experiment are used. After 21 days of oral treatment with of test compound, the rats are anaesthetized and mounted in a stereotaxic instrument. Several groups of rats treated with different doses of the test compound are used. A hole (3 x 3 mm) is drilled in the skull. Recording of DA neurone activity is performed with a single barrel glass electrode. Eight electrode penetrations are made through VTA and SNC, respectively. Data from the experiments

consist of neurone counts which may be regarded as approximately Poisson distributed. The data are expressed as percent active DA neurones of the number of active neurones in non-treated animals. Results are shown in Figs. **1-2** . In addition Comp. **3** inhibited the firing in VTA by 19% and in SNC by 9% at a dose of 2.2 µmol/kg and by 22% in the VTA and by 3% in the SNC at a dose of 4.4 µmol/kg.

The known substances clozapine and haloperidol were included in the test for comparison purposes. Results for these known substances are shown in Figs. **3-4** , respectively.

Results

As described in our copending EP-A2-0465398 the indole and 2,3-dihydroindole derivatives used according to the invention in general potently bind to 5-HT_2 receptors with nanomolar affinities (^{3}H-ketanserin binding test), whereas they have substantially no affinity to the DA D_2 receptors (^{3}H-spiperone binding test). The quipazine-inhibition test showed that the present indole compounds have potent central 5-HT_2 antagonism *in vivo* with good oral bioavailability and long duration of action. Furthermore it was found that the compounds have no central antidopaminergic activity *in vivo* as measured by the inhibition of pergolide-induced rotations in rats with unilateral 6-OHDA lesions, which test is an extremely sensitive test for DA D_2 antagonistic activity *in vivo* (Arnt, J. and J. Hyttel, *J. Neural. Transm.*, **1986** ,*67* , 225-240).

The test for inhibition of the firing of DA neurones in the VTA and SNC, respectively showed that the compounds used in the present invention inhibits the firing in the VTA. As seen from Figs. **1-2** and the data for Comp. **3**, the compounds tested caused a partial inhibition of the firing in the VTA, whereas they had substantially no activity in the SNC area in relevant doses. From Figs. **3-4** it appears that haloperidol inhibits the firing equipotently in both areas whereas clozapine, like the compounds of the invention, inhibits the firing partially and selectively in the VTA, though it is only active in high doses.

FORMULATION EXAMPLES

Typical examples of formulas for compositions manufactured according to the invention, are as follows:

1) Tablets containing 0.5 milligrams of **Comp. 1** calculated as the free base:

Comp. 1	0.5 mg
Lactose	18 mg
Potato starch	27 mg
Saccharose	58 mg
Sorbitol	3 mg
Talcum	5 mg
Gelatine	2 mg
Povidone	1 mg
Magnesium stearate	0.5 mg

2) Tablets containing 5.0 milligrams of **Comp. 1** calculated as the free base:

Comp. 1	5.0 mg
Lactose	16 mg
Potato starch	45 mg
Saccharose	106 mg
Sorbitol	6 mg
Talcum	9 mg
Gelatine	4 mg
Povidone	3 mg
Magnesium stearate	0.6 mg

3) Syrup containing per milliliter:

Comp. 2	10.0 mg
Sorbitol	500 mg
Tragacanth	7 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 ml
Water	ad 1 ml

4) Solution for injection containing per milliliter:

Comp. 2	20.0 mg
Acetic acid	17.9 mg
Sterile water	ad 1 ml

5) Solution for injection containing per milliliter:

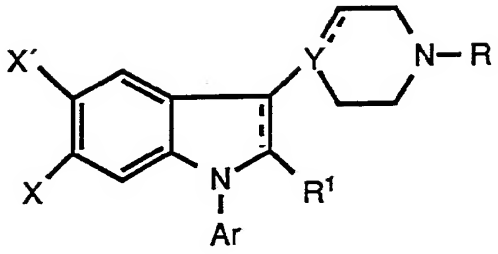
Comp. 1	50.0 mg
Sorbitol	42.9 mg
Acetic acid	0.63 mg
Sodium hydroxide	22 mg
Sterile water	ad I ml

Any other pharmaceutical tableting adjuvants may be used provided that they are compatible with the active ingredient, and additional compositions and dosage forms may be similar to those presently used for neuroleptics, such as clopenthixol, flupentixol or fluphenazine.

Also combinations of the compounds as well as their non-toxic acid salts with other active ingredients, especially other neuroleptics, thymoleptics, tranquilizers, analgesics or the like,fall within the scope of the present invention.

CLAIMS

1. Use of a 6- and/or 2-substituted 1-arylindole derivative having the general Formula I :



I.

where Ar is phenyl, phenyl substituted with one or more substituents selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, hydroxy, trifluoromethyl, and cyano, or a hetero aromatic group selected from 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-oxazolyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl;

the dotted lines indicate optional bonds;

X is hydrogen, halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, hydroxy, C_1-C_4-alkylthio, C_1-C_4-alkylsulfonyl, C_1-C_4-alkyl- or di-(C_1-C_4)-alkylamino, cyano, trifluoromethyl, or trifluoromethylthio;

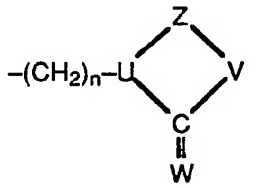
X′ is a substituent taken from the X-substituents above; or
X and X′ are linked to constitute a 5-7 membered carbocyclic ring;

R^1 is hydrogen, C_1-C_4-alkyl or C_1-C_4-alkyl substituted with one or two hydroxy groups, provided that when X is hydrogen or fluoro, then R^1 is not hydrogen;

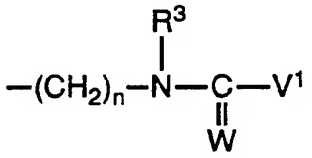
Y is nitrogen or carbon, provided that when the dotted line emanating from Y indicates a bond, then Y is carbon;

R is hydrogen, or C_1-C_4-alkyl, C_2-C_4-alkenyl, cycloalkyl, or cycloalkylmethyl, each

optionally substituted with one or two hydroxy groups, any hydroxy group present being optionally esterified with an aliphatic carboxylic acid having from two to twentyfour carbon atoms inclusive, or R is a substituent of the formula **1a** or **1b** :



1a.



1b.

wherein n is an integer from 2 - 6, inclusive;

W is oxygen or sulfur;

U is nitrogen or carbon;

Z is selected from $-(CH_2)_m-$, m being 2 or 3, -CH=CH- , $-COCH_2-$, $-CSCH_2-$, 1,2-phenylene and 1,2-phenylene substituted with halogen or trifluoromethyl;

V is selected from oxygen, sulfur, CH_2, and NR^2 , wherein R^2 is hydrogen, C_1-C_4-alkyl, C_2-C_4-alkenyl, a cycloalkyl group, a cycloalkylmethyl group, C_1-C_4-alkyl substituted with one or two hydroxy groups, and C_2-C_4-alkenyl substituted with one or two hydroxy groups;

V^1 is $-O-R^4$, $-S-R^4$, $-CHR^4R^5$ or $-NR^4R^5$;

R^3 is hydrogen, C_1-C_4-alkyl, C_2-C_4-alkenyl, a cycloalkyl group, a cycloalkylmethyl group, C_1-C_4-alkyl substituted with one or two hydroxy groups, and C_2-C_4-alkenyl substituted with one or two hydroxy groups; and

R^4 and R^5 are independently selected from the R^3-substituents;

or a pharmaceutically acceptable acid addition salt or prodrug thereof, for the manufacture of a pharmaceutical composition for the treatment of psychoses in humans.

2. A use according to Claim 1, characterized in that the compound used is selected from:

6-chloro-1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole,

6-chloro-1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, and

5-chloro-1-(4-fluorophenyl)-2-methyl-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole.

3. A method for the treatment of psychoses in humans comprising the step of administering a therapeutically effective amount of a 6- and/or 2-substituted 1-arylindole derivative having the general Formula **I** as defined in Claim **1** or a pharmaceutically acceptable acid addition salt or prodrug thereof to a patient in need thereof.

4. A method for the treatment of psychoses in humans comprising the step of administering a therapeutically effective amount of a 6- and/or 2-substituted 1-arylindole derivative as defined in Claim **2** or a pharmaceutically acceptable acid addition salt or prodrug thereof to a patient in need thereof.

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UPON FILING

Fig. 3.

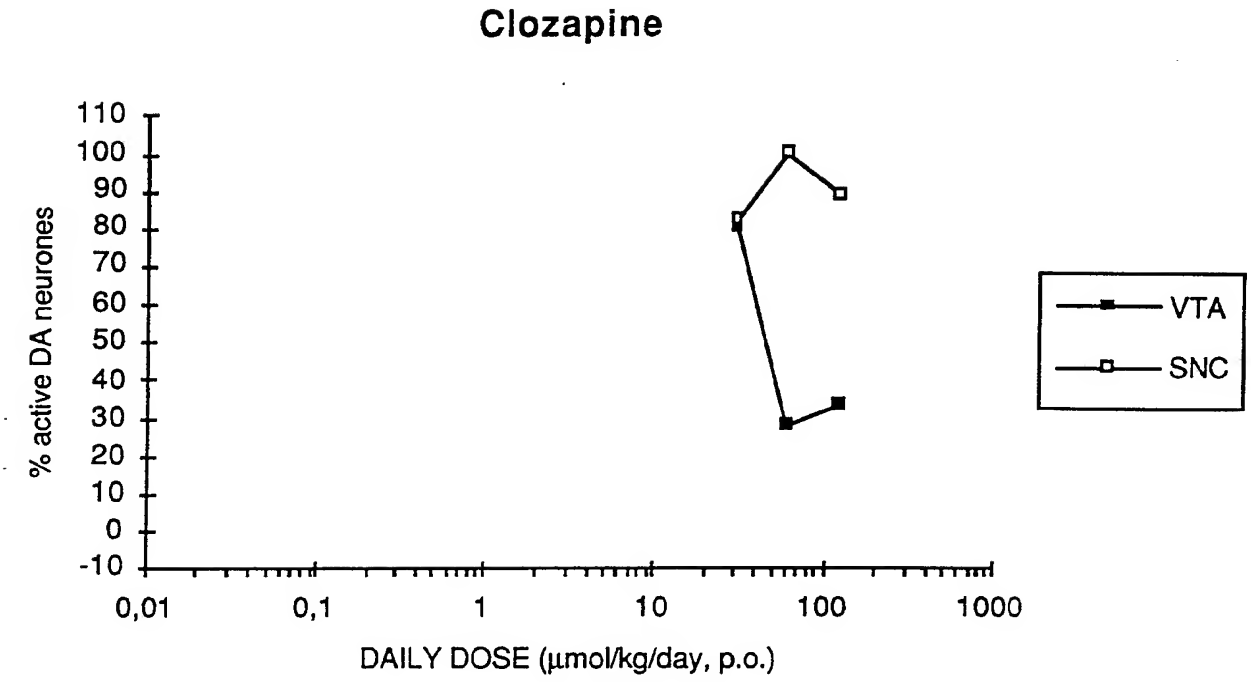
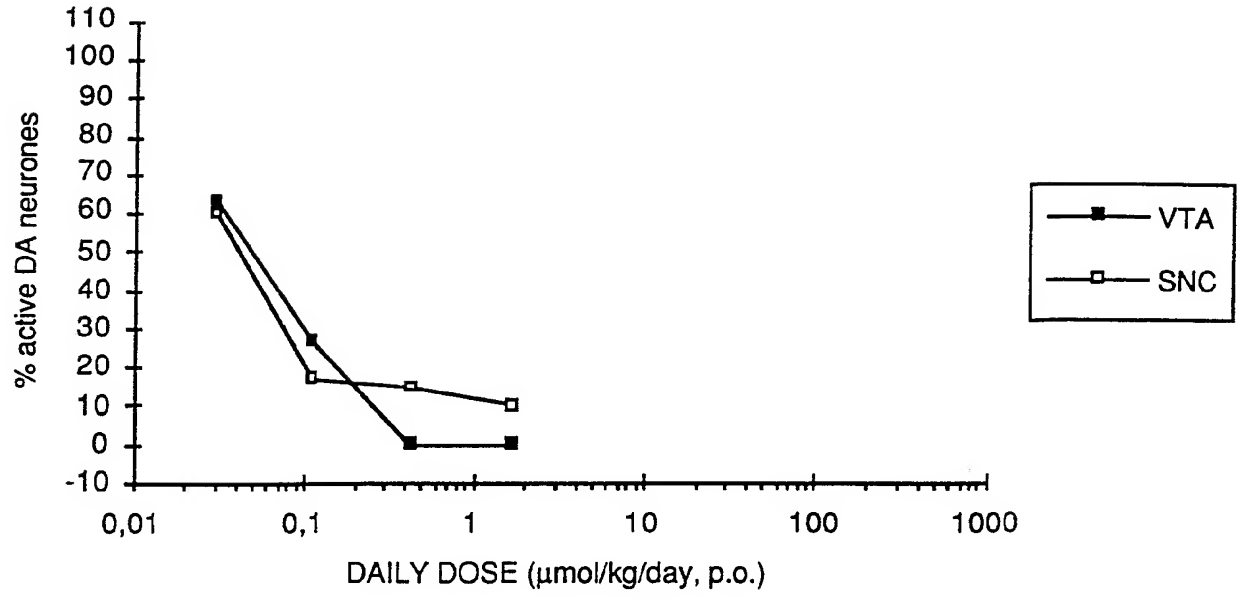

Clozapine
% active DA neurones
110
100
90
80
70
60
50
40
30
20
10
0
-10
0,01
0,1
1
10
100
1000
DAILY DOSE (µmol/kg/day, p.o.)
VTA
SNC

Fig. 4


Haloperidol
% active DA neurones
110
100
90
80
70
60
50
40
30
20
10
0
-10
0,01
0,1
1
10
100
1000
DAILY DOSE (µmol/kg/day, p.o.)
VTA
SNC

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 92/00390

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 31/445, A61K 31/505
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A2, 0392959 (H. LUNDBECK A/S), 17 October 1990 (17.10.90) --	1-2
P,X	WO, A1, 206089 (H. LUNDBECK A/S), 16 April 1992 (16.04.92) --	1-2
P,X	EP, A2, 465398 (H. LUNDBECK A/S), 8 January 1992 (08.01.92) --	1-2
A	US, A, 4710500 (JENS K. PERREGAARD), 1 December 1987 (01.12.87) -- --------	1-2

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 March 1993	30 -03- 1993
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carolina Gómez Lagerlöf Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

Ir. ational application No.
PCT/DK 92/00390

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 3-4
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

26/02/93

International application No.
PCT/DK 92/00390

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A2- 0392959	17/10/90	AU-B- 621735	19/03/92
		AU-A- 5303790	18/10/90
		JP-A- 2290872	30/11/90
		US-A- 5112838	12/05/92
WO-A1- 206089	16/04/92	NONE	
EP-A2- 465398	08/01/92	NONE	
US-A- 4710500	01/12/87	AU-B- 583607	04/05/89
		CA-A- 1256437	27/06/89
		EP-A,B- 0200322	05/11/86
		SE-T3- 0200322	